Conclusions: Synthesis of chemically modified insulin with hydrolyzable amphiphillic oligomers has been accomplished. Products formulated in microemulsion have been evaluated orally in diabetic (i.e., pancreatectomized) dogs. Prolonged glucose reduction following oral administration of the insulin-oligomer products has been achieved.

We claim:

1. A drug-oligomer conjugate having the following general formula:

$$D—[(H—S_n)—L_o]_p \quad \text{(Formula 11)}$$

wherein

D is a therapeutic drug moiety;

H is a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2–24 carbon atoms, cholesterol, adamantane and fatty acids;

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

n is a number from 1 to the maximum number of covalent bonding sites at which S can form a bond with H;

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with S;

p is a number from 1 to the maximum number of covalent bonding sites at which —[(H—Sn)—Lo] can form a bond with D; and

the S—H bond is hydrolyzable.

2. The drug-oligomer conjugate of claim **1** wherein L is selected so as to render the $D—[(H—S_n)—L_o]_p$ conjugate inactive prior to hydrolysis of the S—H bond.

3. The drug-oligomer conjugate of claim **1** wherein the L—S bond is hydrolyzable, and wherein L is selected so as to render the $D—[(H—S_n)—L_o]_p$ conjugate inactive prior to hydrolysis of the S—L bond.

4. The drug-oligomer conjugate of claim **1** wherein D is insulin or a functional equivalent thereof.

5. A drug-oligomer conjugate having the following general formula:

$$D—[(H—S_n—H'_q)—L_o]_p \quad \text{(Formula 12)}$$

wherein

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2–24 carbon atoms, cholesterol, adamantane and fatty acids;

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

n is a number from 1 to the maximum number of covalent bonding sites at which S can form a bond with H;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can form a bond with S;

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with S;

p is a number from 1 to the maximum number of covalent bonding sites at which $—[(H—S_n—H'_q)—L_o]$ can form a bond with D; and

the H—S bond is hydrolyzable.

6. The drug oligomer conjugate of claim **5** wherein L is selected so as to render the $D—[(H—S_n—H'_q)—L_o]_p$ conjugate inactive prior to hydrolysis of the H—S bond.

7. The drug-oligomer conjugate of claim **5** wherein the S—H' bond is hydrolyzable, and wherein L is selected so as to render the $D—[(H—S_n—H'_q)—L_o]_p$ conjugate inactive prior to hydrolysis of the S—H' bond.

8. The drug-oligomer conjugate of claim **5** wherein the H'—L bond is hydrolyzable, and wherein L is selected so as to render the $D—[(H—S_n—H'_q)—L_o]_p$ conjugate inactive prior to hydrolysis of the H'—L bond.

9. The drug-oligomer conjugate of claim **5** wherein the H'—L bond is non-hydrolyzable, and wherein the $(H—S_n—H'_q)—L_o$ oligomer comprises an H'—L subunit selected from the group consisting of:

$$CH_3(CH_2)_n(OC_2H_4)_mOH \quad \text{(Formula 3)}$$

wherein n=3 to 25 and m=1 to 7;

$$CH_3(CH_2)_n(OC_2H_4)_mOCH_2CO_2H \quad \text{(Formula 4)}$$

wherein n=3 to 25 and m=1 to 6;

$$R—(OC_2H_4)_mCH_2CO_2H \quad \text{(Formula 6)}$$

wherein m=0 to 5 and R=cholesterol or adamantane;

$$CH_3(CH_2—CH=CH)_6(CH_2)_2(OC_2H_4)_mOH \quad \text{(Formula 8)}$$

wherein m=1 to 7; and

$$CH_3(CH_2—CH=CH)_6(CH_2)_2CX(OC_2H_4)_mOH \quad \text{(Formula 9)}$$

wherein m=1 to 7 and X=NH.

10. The drug-oligomer conjugate of claim **5** wherein D is insulin or a functional equivalent thereof.

11. A drug-oligomer conjugate having the following general formula:

$$D—[(H—H'_q—S_n)—L_o]_p \quad \text{(Formula 13)}$$

wherein

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2–24 carbon atoms, cholesterol, and fatty acids;

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can form a bond with H;

n is a number from 1 to the maximum number of covalent bonding sites at which S can form a bond with H';

o is a number from 1 to the maximum number of covalent bonding sites at which L can form a bond with S;

p is a number from 1 to the maximum number of covalent bonding sites at which $—[(H—H'_q—S_n)—L_o]$ can form a bond with D; and

the H—S bond is hydrolyzable.

12. The drug-oligomer conjugate of claim **11** wherein D is insulin or a functional equivalent thereof.

13. The drug-oligomer conjugate of claim **11** wherein D is insulin or a functional equivalent thereof and H is PEG_{2-7}.

14. The drug-oligomer conjugate of claim **11** wherein D is insulin or a functional equivalent thereof and H is PEG_3.